Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

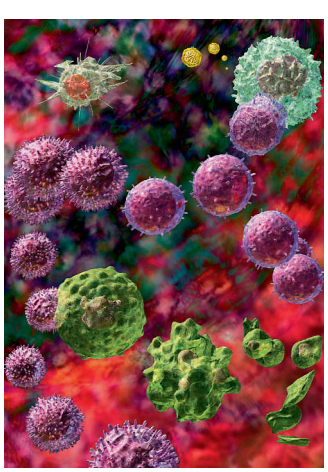
examining the precise balance of the immune system's different components.

Sunil Ahuja's team at the University of Texas Health Science Center, for example, has designed a way to classify people's "immune grade" based on the relative levels of different T-cells. People with higher-than-average numbers of helper T-cells, combined with lower levels of killer T-cells, had the highest immune grade, according to their classification. The team has shown that people with immune grade I tend to have much better outcomes when they face a pathogen, with 88 per cent reduced mortality compared with those of lower grades after a covid-19 infection, for instance.

Importantly, the team's grades proved to be a better predictor for response to covid-19 than age alone, meaning that, in the future, this kind of measure may help to identify high-risk individuals with greater precision (see "How does your immune system change as you age?", page 43). "Even if you are 80, and you have a high immune grade, you'll do much better than someone much younger with a low immune grade," says Ahuja.

You may need to wait a while before your doctor is able to assess your health with this kind of precision, but you can get a good idea about the state of your immune system without any tests. As a general rule of thumb, Macciochi says that the average person should expect to have one or two mild illnesses a year. If you tend to become sick far more often, and if those infections tend to last much longer and are more severe than the people around you, then it may be a sign that one or more of the units in your immune army aren't functioning as they should. Your doctor should be your first port of call, but there are also things you can do to give your immunity a helping hand (see "What should you eat to boost your immune system?", page 41).

David Robson



RUSSELL KIGHTLEY/SCIENCE PHOTO LIBRARY

White blood cells can help to indicate immune health

WHAT EFFECT DID LOCKDOWNS HAVE ON CHILDREN'S IMMUNE SYSTEMS?

IT IS a question high in the minds of many parents and carers of infants born during the first years of the covid-19 pandemic: have lockdowns and social distancing had a long-term effect on babies' health? The good news is that these concerns are largely underpinned by misunderstandings over how the immune system is shaped during our first years of life.

It is clear that pandemic public health measures have had an impact on children's exposure to bacteria and viruses that cause illness. When strict social distancing rules were in place, the capacity for infections to spread was dramatically reduced.

An analysis of data from across England found that the number of children below the age of 15 admitted to hospital with influenza between March 2020 and June 2021 dropped by 94 per cent. It wasn't just flu that was affected: the analysis found reductions in child hospitalisations in 18 of the 19 infections they looked at, including mumps, measles, croup, tonsillitis and bronchiolitis.

Fewer infections

This leaves lockdown babies in a different position to the average infant. Typically, around 90 per cent of UK children have had an infection by the age of 1, for instance, but an analysis of babies born during Ireland's first lockdown found that less than half of 12-month-olds experienced any infections during their first year.

Fortunately, we don't actually need to get sick when we are very young. Infections like flu are more likely to lead to serious complications, such as pneumonia, in young children, especially those under the age of 2. "If you can avoid disease, it's better if you avoid it," says Nikolaos Papadopoulos at the University of Manchester, UK.

In recent months, the northern hemisphere has had a difficult winter in terms of seasonal infections, including among children. Lower population immunity is partly to blame for surging levels of illness caused by pathogens like the flu virus and RSV: because there were fewer cases of these illnesses during strict covid-19 measures, numbers are catching up now. This isn't a sign that children's immune systems have been weakened by lockdowns.

JEAN GAUMY/MAGNUM PHOTOS

The idea that it is important to get infections during infancy comes from the hygiene hypothesis, first proposed by epidemiologist David Strachan in 1989. The thinking was that life had become more hygienic, leading children to catch fewer infections, and that this predisposed them to develop allergies. But while the idea that young immune systems need to be "trained" on pathogens has taken hold in the public consciousness, the hygiene hypothesis isn't our best way of understanding immune systems in the modern age. What we really need in early life is to encounter a wide diversity of microbes – and not just the ones that are bad for you.

The ideal scenario, says Papadopoulos, is to be exposed "in very small quantities to many different types of microbes, viruses and bacteria, below the threshold for disease". So, rather than being a good thing in itself, getting ill is more of a marker that your child is encountering a range of microbes, good and bad. If you don't encounter many pathogens in your first years, that doesn't mean you will be less good at fighting them off later on, because your immune system continues to learn about diseases throughout life.

However, our early years do seem to be important for shaping our response to allergens, and a lack of exposure to diverse microbes during this time may make children more susceptible to allergies,

The number of children hospitalised for severe infections dropped in 2020-2021

asthma and some types of eczema. The Irish study found that lockdown babies were more likely to have atopic eczema and show signs of sensitisation to egg – the first step towards an allergy – although there was no increase in the proportion of children who actually had an egg allergy by the age of 1.

However, there are other ways we receive early microbial exposure than just socialising. Some, such as being born vaginally rather than by C-section, may not have been affected by the pandemic. Others, such as breastfeeding, spending time outside, antibiotic use and even living with a pet dog, may have been influenced by the way our lives changed in 2020 and 2021 – positively for some, negatively for others.

At the same time, while we know that all these factors seem to be linked to immune functioning, none of them has a strong enough effect to fully determine your immune future. It will be shaped by a complex interplay of personal circumstances, including genetics and many small and unique differences in the microbial environments in which we grow up. Which, thankfully, means there is no "right" way to train a young immune system.

Penny Sarchet

HOW TO TRAIN THE IMMUNE SYSTEM TO CURE SEVERE DISEASE

ONE of the most amazing things about the immune system is how hard it works without you even being aware. It not only fights off bacteria and viruses every day, it also kills off most cancers long before they become a threat. But sometimes cancers manage to dodge the immune system – and a number of cancer therapies rely on restoring its effectiveness. An emerging star is CAR T-cell therapy, which has produced dramatic results for some cancers when all the usual treatments have failed.

This incredible technology relies on T-cells, immune cells that patrol our body, killing infected or cancerous cells. T-cells detect their targets with a receptor that protrudes from their surface and binds to a target protein, or a displayed fragment of a protein, on the outside of other cells. What this means is that if you add the right receptor to T-cells, you can make them target anything you want, including a cancer.

To achieve this, a person's own T-cells are extracted and genetically modified to express a "chimeric antigen receptor". This artificial receptor is made up of three proteins, one that recognises the cancer cell target and two that boost the T-cells' activity.

Doctors multiply these cells and return them to their owner, where they seek out and destroy cells that have the target protein.

With a few of the first people treated still remaining free of cancer a decade later, it can now be said that, in some cases, CAR T-cell therapies can cure advanced cancers.

Unfortunately, this approach isn't a magic bullet. For starters, the immune attack on cancer cells it prompts can trigger potentially fatal side effects. What's more, CAR T-cells only work against blood cancers, not solid tumours, and only in a minority of people.

But there is hope. The technique is being improved. One big issue is that having to use each individual's own T-cells is extremely expensive, and with very ill people, it isn't always possible to extract enough T-cells. Donor T-cells see every cell in the recipient's body as foreign and start attacking them.

So, gene editing is now being used to knock out the genes involved in recognising cells as foreign, in addition to adding the receptor. These universal CAR T-cells can be used to treat many different people with the same cancers.

Leukaemia success

Another issue is that T-cells have an off switch on their surface called PD-1 to help prevent them attacking healthy cells. Some cancers thwart T-cell attacks by exploiting this switch. But if it is removed via gene editing, the T-cells can't be deactivated.

With standard gene editing, there is a limit to the number of changes that can be made. This is because each edit requires cutting DNA, which can kill cells or result in major mutations. But the latest CRISPR gene-editing tools don't cut DNA and so allow more changes to be made safely.

This approach was used last year to treat T-cell leukaemia for the first time. The 13-year-old who received the treatment had aggressive leukaemia that hadn't responded to any other therapy. Twenty-eight days later, tests revealed she was in remission.

Other teams are introducing even more ambitious changes to CAR T-cells in the hope of making them effective against solid tumours too. The use of CAR T-cells for treating infections by pathogens such as HIV and hepatitis C is also being explored. Furthermore, CAR T-cells are being used to treat autoimmune diseases by killing off the rogue immune cells responsible. Last year, a team in Germany reported that five people with lupus have remained free of the disease since being treated this way.

Genetically engineered immune cells are going to be a big part of our future. It is a future that looks very bright indeed.

Michael Le Page

"The average person should expect one or two mild illnesses a year"